1615

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Maurer, et al.	
Application No.: 10/019,199	Group Art Unit: 1615
Filed: 12/20/2001	Examiner: G.S. Kishore
Title: Methods for Preparation of Lipid-Encapsulated Therapeutic Agents	Confirmation No: 6234
Attorney Docket No.: INEX.P-005	
Customer No.: 021121	

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Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RESPONSE TO OFFICIAL ACTION

Dear Sir:

This is in response to the Office Action mailed June 27, 2003 for the above-captioned application. Reconsideration and further examination are respectfully requested.

Claims 13-32 are pending in this application.

The Examiner rejected claims 13-32 under 35 USC § 103 as obvious over the combination of US Patent No. 6,447,800 of Hope et al. and US Patent No. 5,976,567 of Wheeler or WO 98/51278.

I hereby certify that this paper and any attachments named herein are transmitted to the United States Patent and Trademark Office, Fax number: 703-872-9306 on September 26, 2003.

Marina T Larson

Marina T. Larson, PTO Reg. No. 32,038

September 26, 2003
Date of Signature

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In assessing the appropriateness of a rejection under 35 USC § 103, it is important to remember that merely finding the various elements distributed among several pieces of art is not sufficient to support a rejection. Indeed, as the Patent Office Board of Appeals has observed, "citing references which merely indicate the isolated elements ... are known is not a sufficient basis for concluding that the combination of elements would have been obvious." *Ex Parte Hiyamizu*, 10 USPQ 2d 1393, 1394 (POBAI 1988) What is required in addition to teaching of the various elements is some motivation in the art, not in the application under examination, to make the combination of elements as set forth in the claims. The rejection of claims 13-32 based on Hope and Wheeler or WO98/51278 does not meet this standard.

The need to evaluate the combination from the perspective of a person skilled in the art, and not simply as a combination of elements, is particularly acute in considering lipid compositions. Interactions of lipids with one another and with non-lipid components in the same mixture are complex. Further, the purposes for which lipid composition are prepared are diverse, and the requirements for these different purposes are not the same. When these factors are taken into account, it is clear that the references which the Examiner has cited would not have suggested the present invention to a person skilled in the art.

Like the present method, Hope deals with a method of loading liposomes, that is of introducing material into the lumen or interior of the liposome. It accomplishes this by combining pre-formed liposomes, the active agent and ethanol. The ethanol acts to permeabilize the membrane of the liposome. Subsequent dilution of the ethanol (which is comparable to removal of the organic solvent in the present claims) results is a permeability decrease. Hope specifically teaches that "generally, highly negatively charged species such as polynucleotides **do not** cross the liposomal membranes permeabilized by the solvent techniques disclosed herein." (Col. 10, lines 7-10). Further, Hope states that this exclusion is so good that is can be used to entrap neutral species in the presence of charged species to accomplish a separation. (Col. 10, lines 10-13).

The claimed invention is a method for preparing lipid-encapsulated therapeutic agent particles where the therapeutic agent is charged. This includes therapeutic agents that are negatively charged materials such as polynucleotides (see claim 16). Highly efficient encapsulation is achieved with preformed vesicles by incorporation of a charged lipid of opposite charge to the therapeutic agent and a modified lipid with a steric barrier moiety, such a PEG. The Examiner asserts that it would have been obvious to add a cationic lipid to the liposomes of Hope to accomplish the very thing that Hope said was not accomplished by his particles. Applicants respectfully disagree. Further, Applicants note that the rejection does not offer any references with respect to the reverse charge concentration, and that the arguments herein focus on the same combination as the Examiner's rejection. These remarks should not be construed as limiting the scope of the claims.

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As a first matter, Applicants note that Hope was filed subsequent to the priority dates of the two secondary references, and that Michael Hope is an inventor on both of the secondary references as well. Thus, it may be presumed that he was fully aware of formulations containing cationic liposomes at the time the Hope patent was filed, but did not find it obvious that the problem noted in Hope could be solved by the expedient of adding a cationic charged lipid to the liposomes.

Secondly, it is important not to select portions of the references for combination and not consider the overall teaching of the references. Hope's method, and indeed the method of the invention is one in which the solvent, for example ethanol, facilitates passage of the solute into the interior of the preformed liposome. Wheeler on the other hand relates to the formation of lipid - nucleic acid complexes as a result of interaction between the positive and negative charges on the two species. Indeed, Figs. 1-3 of Wheeler graphically illustrate the various ways in which polynucleotides and cationic lipids can stick together. We know from Hope that negatively-charged species do not pass through an uncharged membrane. Why then would a person skilled in the art imagine that negatively charged polynucleotides would pass through a membrane better, when that membrane contains positive charges to which they can stick as shown in Wheeler. Thus, the overall teaching of the references, as opposed to selected elements chosen based on the claimed invention, does not suggest that which is now claimed. WO98/51278 does not offer any different suggestions. In this case, there are no preformed liposomes, as in Hope and as in the claimed invention; and encapsulation occurs around the charged polyunucleotides. There is thus no suggestion that movement into a preformed liposome would become possible for a negatively-charged polynucleotide because of the incorporation of a positively charged lipid in the liposome.

Thirdly, Applicants note that the Examiner has said that the addition of PEG-lipids to the compositions of Hope would have been obvious since WO 98/51278 teaches their ability to provide steric stabilization. What the Examiner has not said, is why one skilled in the art would think that "steric stablization" is needed in the liposomes of Hope. Steric stabilization is used in the reference to reduce or eliminate aggregation of lipid particles. Nothing in Hope indicates that such aggregation would be a problem, nor has the Examiner offered any reasoning as to why a person skilled in the art would anticipate the existence of such problems. Accordingly, there is no motivation in the cited art to include PEG-lipids in the compositions of Hope.

The Examiner also rejected claims 13-32 as unpatentable over Hope in view of Malone and Zalipsky. This rejection is very similar to that discussed above, with Malone providing the teaching of cationic lipid nucleic acid complexes, and Zalipsky offering a teaching concerning PEG-lipids. This rejection is deficient for the same reasons as discussed above.

The Examiner jrected claims13-20 and 25-32 as unpatentable over Schubert in view of Malone and either Zalipsky or WO 98/51278. Schubert is substantially cumulative with Hope,

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except that a different method for opening the membrane of a pre-formed liposome is disclosed. Specifically, in the case of Schubert, sodium cholate, a bile salt, is used to open the membrane. The Examiner has not indicated why a person skilled in the art would anticipate that changing the liposome structure to include a cationic lipid would allow loading of pre-formed lipids with a negatively charged oligonucleotide, without this step of membrane opening being necessary. Further, the reliance on Malone or Zalipsky in this rejection is flawed for the same reasons as discussed above.

For these reasons, Applicants submit that the rejections of record should be withdrawn. This application is now considered to be in condition for allowance and such action is earnestly solicited.

Respectfully Submitted,

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